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Citation: 858 F2d 731

*858 F.2d 731, *; 1988 U.S. App. LEXIS 13208, **;
8 U.S.P.Q.2D (BNA) 1400*

In re JACK R. WANDS, VINCENT R. ZURAWSKI, JR., and HUBERT J. P. SCHOEMAKER

No. 87-1454

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

858 F.2d 731; 1988 U.S. App. LEXIS 13208; 8 U.S.P.Q.2D (BNA) 1400

September 30, 1988, Decided

SUBSEQUENT HISTORY: [1]**

As Amended October 20, 1988.

PRIOR HISTORY:

Appealed from: Patent and Trademark Office, Board of Patent Appeals and Interferences.

CASE SUMMARY

PROCEDURAL POSTURE: Appellant sought review of the decision of the Patent and Trademark Office Board of Patent Appeals and Interferences affirming rejection of appellant's application for a patent under 35 U.S.C.S. § 112 because appellant's written specifications would not enable a person to practice the claimed invention without undue experimentation.


OVERVIEW: Appellants contended that their written specifications fully enabled the practice of their claimed invention in accordance with 35 U.S.C.S. § 112 because the antibodies needed to perform the immunoassays could be made from readily available starting materials using methods that were well known in the antibody art. Respondent alleged that appellant's data presented that the production of antibodies was unpredictable and unreliable and that it would require undue experimentation for one skilled in the art to make the antibodies. The court agreed with appellant, holding that respondent's interpretation of the data was erroneous. Appellant's written disclosure fully enabled the claimed invention. Respondent's classification of the stored cell lines as failures was strained and unduly harsh. Appellant's explanation of its initial failures was reasonable and in view of the fact that the following six fusions were successful, the court concluded that appellant effectively rebutted respondent's challenge to 35 U.S.C.S. § 112.


OUTCOME: The court reversed the decision affirming rejection of appellant's application, concluding that appellant's written specification would not require undue experimentation to obtain antibodies needed to practice the claimed invention in order to meet the enablement requirement.

CORE TERMS: antibody, cell, hybridoma, invention, experimentation, antigen, affinity, undue, binding, monoclonal antibodies, patent, fusion, deposit, lymphocyte, high-affinity, screening, immunoassay, enablement, constant, isotype, specification, determinant, clone, experiment, monoclonal antibody, myeloma, bind, disclosure, stored, cpm


LexisNexis(TM) HEADNOTES - Core Concepts - ♦ Hide Concepts


 Patent Law > Specification & Claims > Definiteness

 Patent Law > Specification & Claims > Enablement Requirement


HN1  The first paragraph of 35 U.S.C.S § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. Patents are written to enable those skilled in the art to practice the invention.


 Patent Law > Specification & Claims > Enablement Requirement

 Patent Law > Specification & Claims > Description Requirement


HN2  A patent need not disclose what is well known in the art.

 Civil Procedure > Appeals > Standards of Review > Clearly Erroneous Review


 Civil Procedure > Appeals > Standards of Review > De Novo Review

HN3  Although the court reviews underlying facts found by the board under a clearly erroneous standard, it reviews enablement as a question of law.


 Patent Law > Specification & Claims > Enablement Requirement

HN4  Although inventions involving microorganisms or other living cells often can be enabled by a deposit, a deposit is not always necessary to satisfy the enablement requirement. No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.


 Patent Law > Specification & Claims > Enablement Requirement

HN5  Whether the specification in an application involving living cells is enabled without a deposit must be decided on the facts of the particular case.


 Patent Law > Specification & Claims > Enablement Requirement

HN6  Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is "undue", not "experimentation."


 Patent Law > Specification & Claims > Enablement Requirement

HN7  The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

 Patent Law > Specification & Claims > Enablement Requirement

HN8  Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.

 Patent Law > Specification & Claims > Enablement Requirement

HN9  Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art,

and (8) the breadth of the claims.

COUNSEL: Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein, of Washington, District of Columbia, argued for Appellant. With him on the brief was Henry N. Wixon.

John H. Raubitschek, Associate Solicitor, Commissioner of Patents and Trademarks, of Arlington, Virginia, argued for Appellee. With him on the brief were Joseph F. Nakamura, Solicitor and Fred E. McKelvey, Deputy Solicitor.

JUDGES: Smith, Newman, and Bissell, Circuit Judges. Newman, Circuit Judge, concurring in part, dissenting in part.

OPINIONBY: SMITH

OPINION: [*733] SMITH, Circuit Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM Antibodies," which was filed September 19, 1980. n1 The rejection under 35 U.S.C. § 112, first paragraph, is based on the grounds that appellant's written specification would not enable [**2] a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We reverse.

-----Footnotes-----

n1 *In re Wands*, Appeal No. 673-76 (Bd. Pat. App. & Int. Dec. 30, 1986).

-----End Footnotes-----

I. Issue

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, of all remaining claims in appellants' patent application, serial No. 188,735.

II. Background

A. The Art.

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. *Antibodies* are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an *antigen*. The body has the ability to make millions of [**3] different antibodies that bind to different antigens. However, it is only after exposure to an antigen that a complicated *immune response* leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called *hepatitis B surface antigen* (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as reagents for sensitive diagnostic tests (e.g., to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an *immunoassay*.

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with **[**4]** which they bind to the determinant. *Affinity* is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or *isotypes*. Immunoglobulin G (IgG) is the most common isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only antibodies.

For commercial applications there are many disadvantages to using antibodies from serum. Serum contains a complex mixture of antibodies against the antigen of interest within a larger pool of antibodies directed at other antigens. These are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.

The blood cells that make antibodies are *lymphocytes*. Each **[**5]** lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to **[*734]** their particular antigen divide and mature. Each produces a *clone* of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture.

Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of *myeloma* cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma **[**6]** cells (i.e., by hybridoma cells that are all progeny of a single cell) are called monoclonal antibodies. n2

-----Footnotes-----

n2 For a concise description of monoclonal antibodies and their use in immunoassay see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1368-71, 231 USPQ 81, 82-83 (Fed. Cir. 1986), cert. denied, 480 U.S. 947, 107 S. Ct. 1606, 94 L. Ed. 2d 792 (1987).

-----End Footnotes-----

B. The Claimed Invention.

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent'), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on appeal. The specification of the **[**7]** '145 patent teaches a procedure for immunizing mice

against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. § 112, first paragraph, a hybridoma cell line that secretes IgM antibodies against HBsAg (the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available to the public when the '145 patent issued.

The application on appeal claims methods for immunoassay of HBsAg using monoclonal antibodies such as those described in the '145 patent. Most immunoassay methods have used monoclonal antibodies of the IgG isotype. IgM antibodies were disfavored in the prior art because of their sensitivity to reducing agents and their tendency to self-aggregate and precipitate. Appellants found that their monoclonal IgM antibodies could be used for immunoassay of HbsAg with unexpectedly high sensitivity and specificity. Claims 1, 3, 7, **[**8]** 8, 14, and 15 are drawn to methods for the immunoassay of HBsAg using high-affinity IgM monoclonal antibodies. Claims 19 and 25-27 are for chemically modified (e.g., radioactively labeled) monoclonal IgM antibodies used in the assays. The broadest method claim reads:

1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:

contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and

determining the presence of said substance in said sample;

wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^{9} M^{-1}$.

Certain claims were rejected under 35 U.S.C. § 103; these rejections have not **[*735]** appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25-27 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the disclosure would not enable a person skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely **[**9]** to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

III. Analysis

A. Enablement by Deposit of Microorganisms and Cell Lines.

HN1 ¶ The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents * * * are written to enable those skilled in the art to practice the invention." n3 **HN2** ¶ A patent need not disclose what is well known in the art. n4 **HN3** ¶ Although we review underlying facts found by the board under a "clearly erroneous" standard, n5 we review **[**10]** enablement as a question of law. n6

-----Footnotes-----

n3 W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983), cert. denied, 469 U.S. 851, 105 S. Ct. 172, 83 L. Ed. 2d 107 (1984).

n4 Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

n5 Coleman v. Dines, 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed. Cir. 1985).

n6 Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986), cert. denied, 479 U.S. 1030, 107 S. Ct. 875, 93 L. Ed. 2d 829 (1987); Raytheon Co. v. Roper Corp., 724 F.2d 951, 960 n.6, 220 USPQ 592, 599 n.6 (Fed. Cir. 1983), cert. denied, 469 U.S. 835, 83 L. Ed. 2d 69, 105 S. Ct. 127 (1984).

-----End Footnotes-----

Where an invention depends on the use of living materials such as microorganisms or cultured cells, it may be impossible **[**11]** to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues. n7 Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112. n8 A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public. n9 Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials. n10

-----Footnotes-----

N7 In re Argoudelis, 58 C.C.P.A. 769, 434 F.2d 1390, 1392-93, 168 USPQ 99, 101-02 (CCPA 1970).

n8 In re Lundak, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985); Feldman v. Aunstrup, 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), cert. denied, 424 U.S. 912, 47 L. Ed. 2d 316, 96 S. Ct. 1109 (1976); Manual of Patent Examining Procedure (MPEP) 608.01(p)(C) (5th ed. 1983, rev. 1987). See generally Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J. Pat. Trademark Off. Soc'y 569 (1985). **[**12]**

n9 In re Jackson, 217 USPQ 804, 807-08 (Bd. App. 1982) (strains of a newly discovered species of bacteria isolated from nature); Feldman, 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); In re Argoudelis, 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); In re Kropp, 143 USPQ 148, 152 (Bd. App. 1959) (newly discovered microorganism isolated from soil).

n10 In re Forman, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); In re Lundak, 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).

-----End Footnotes-----

In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the prima facie date of invention, n11

[*736] and to satisfy the requirement under 35 U.S.C. § 114 **[**13]** that the PTO be guaranteed access to the invention during pendency of the application. n12 Although a deposit may serve these purposes, we recognized, in *In re Lundak*, n13 that these purposes, nevertheless, may be met in ways other than by making a deposit.

-----Footnotes-----

n11 *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman*, 517 F.2d at 1355, 186 USPQ at 113; *In re Argoudelis*, 434 F.2d at 1394-96, 168 USPQ at 103-04 (Baldwin, J. concurring).

n12 *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman*, 517 F.2d at 1354, 186 USPQ at 112.

n13 *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96.

-----End Footnotes-----

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, **[**14]** although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

B. Undue Experimentation.

^{HN4} Although inventions involving microorganisms or other living cells often can be enabled by a deposit, n14 a deposit is not always necessary to satisfy the enablement requirement. n15 No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation. n16 ^{HN5} Whether the specification in an application involving living cells (here, hybridomas) is enabled without **[**15]** a deposit must be decided on the facts of the particular case. n17

-----Footnotes-----

n14 *In re Argoudelis*, 434 F.2d at 1393, 168 USPQ at 102.

n15 *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).

n16 *Id.* at 1186-87, 194 USPQ at 525; *Merck & Co. v. Chase Chem. Co.*, 273 F. Supp. 68, 155 USPQ 139, 146 (D.N.J. 1967); *Guaranty Trust Co. v. Union Solvents Corp.*, 54 F.2d 400, 403-06, 12 U.S.P.Q. (BNA) 47, 50-53 (D. Del. 1931), *aff'd*, 61 F.2d 1041, 15 U.S.P.Q. (BNA) 237 (3d Cir. 1932), *cert. denied*, 288 U.S. 614, 77 L. Ed. 987, 53 S. Ct. 405 (1933); MPEP 608.01(p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").

n17 *In re Jackson*, 217 USPQ at 807; see *In re Metcalfe*, 56 C.C.P.A. 1191, 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).

-----End Footnotes-----

Appellants contend that their written specification fully **[**16]** enables the practice of their claimed invention because the monoclonal antibodies needed to perform the immunoassays can be made from readily available starting materials using methods that are well known in the monoclonal antibody art. Wands states that application of these methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation. There is no challenge to their contention that the starting materials (i.e., mice, HBsAg antigen, and myeloma cells) are available to the public. The PTO concedes that the methods used to prepare hybridomas and to screen them for high-affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed in the '145 patent and in the current application. This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980. n18 The sole issue is whether, in this particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies.

-----Footnotes-----

n18 *Hybritech*, 802 F.2d at 1384, 231 USPQ at 94.

-----End Footnotes----- ^{HN6} **[**17]**

Enablement is not precluded by the necessity for some experimentation such as **[*737]** routine screening. n19 However, experimentation needed to practice the invention must not be undue experimentation. n20 "The key word is 'undue,' not 'experimentation.'" n21

^{HN7} The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), cert. denied, 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed * * *. n22

-----Footnotes-----

n19 *Id.*; *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); *In re Angstadt*, 537 F.2d at 502-504, 190 USPQ at 218; *In re Geerdes*, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71, 61 L. Ed. 286, 37 S. Ct. 82 (1916). **[**18]**

n20 *Hybritech*, 802 F.2d at 1384, 231 USPQ at 94; *W.L. Gore*, 721 F.2d at 1557, 220 USPQ at 316; *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (Miller, J., concurring).

n21 *In re Angstadt*, 537 F.2d at 504, 190 USPQ at 219.

n22 *In re Jackson*, 217 USPQ at 807.

-----End Footnotes-----

The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. n23 ^{HN8} Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that **[**19]** should be drawn from that data.

-----Footnotes-----

n23 See *Hybritech*, 802 F.2d at 1384, 231 USPQ at 94; *Atlas Powder*, 750 F.2d at 1576, 224 USPQ at 413.

-----End Footnotes----- ^{HN9}

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *In re Forman*. n24 They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. n25

-----Footnotes-----

n24 *In re Forman*, 230 USPQ at 547.

n25 *Id.*; see *In re Colianni*, 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).

-----End Footnotes----- **[**20]**

In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. The '145 patent provides a detailed description of procedures for immunizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.

The first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells. The cells are cultured in a medium in which all the lymphocytes and myeloma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies **[*738]** that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide. **[**21]** After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest.

Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioactivity bound gives some indication of the strength of the antibody-antigen binding, but does not yield a

numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least $10^{<9> M^{<-1>}}$. n26 The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.

-----Footnotes-----

n26 The examiner, the board, and Wands all point out that, technically, the strength of antibody-HBsAg binding is measured as *avidity*, which takes into account multiple determinants on the HBsAg molecule, rather than affinity. Nevertheless, despite this correction, all parties then continued to use the term "affinity." We will use the terminology of the parties. Following the usage of the parties, we will also use the term "high-affinity" as essentially synonymous with "having a binding affinity constant of at least $10^{<9> M^{<-1>}}$."

-----End Footnotes----- **[**22]**

During prosecution Wands submitted a declaration under 37 C.F.R. § 1.132 providing information about all of the hybridomas that appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas that made antibodies specific for HBsAg. Antibodies that bound at least 10,000 cpm in the commercial radioimmunoassay were classified as "high binders." Using this criterion, 143 high-binding hybridomas were obtained. In the declaration, Wands stated that n27

It is generally accepted in the art that, among those antibodies which are binders with 50,000 cpm or higher, there is a very high likelihood that high affinity (K_a [greater than] $10^{<9> M^{<-1>}}$) antibodies will be found. However, high affinity antibodies can also be found among high binders of between 10,000 and 50,000, as is clearly demonstrated in the Table.

The PTO has not challenged this statement.

-----Footnotes-----

n27 A table in the declaration presented the binding data for antibodies from every cell line. Values ranged from 13,867 to 125,204 cpm, and a substantial proportion of the antibodies showed binding greater than 50,000 cpm. In confirmation of Dr. Wand's statement, two antibodies with binding less than 25,000 cpm were found to have affinity constants greater than $10^{<9> M^{<-1>}}$.

-----End Footnotes----- **[**23]**

The declaration stated that a few of the high-binding monoclonal antibodies from two fusions were chosen for further screening. The remainder of the antibodies and the hybridomas that produced them were saved by freezing. Only nine antibodies were subjected to further analysis. Four (three from one fusion and one from another fusion) fell within the claims, that is, were IgM antibodies and had a binding affinity constant of at least $10^{<9> M^{<-1>}}$. Of the remaining five antibodies, three were found to be IgG, while the other two were IgM for which the affinity constants were not measured (although both showed binding well above 50,000 cpm).

Apparently none of the frozen cell lines received any further analysis. The declaration explains that after useful high-affinity IgM monoclonal antibodies to HBsAg had been found, it was considered unnecessary to return to the stored antibodies to screen for more IgMs. Wands says that the existence of the stored hybridomas was disclosed to the PTO to comply with the requirement under 37 C.F.R. § 1.56 that applicants fully disclose all of their relevant [*739] data, and not just favorable results. n28 How these stored hybridomas are viewed [**24] is central to the positions of the parties.

-----Footnotes-----

n28 See *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 220 USPQ 289 (Fed. Cir. 1983).

-----End Footnotes-----

The position of the board emphasizes the fact that since the stored cell lines were not completely tested, there is no proof that any of them are IgM antibodies with a binding affinity constant of at least $10^{9.5}$ M⁻¹. Thus, only 4 out of 143 hybridomas, or 2.8 percent, were *proved* to fall within the claims. Furthermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the board as evidence that appellants' methods were not predictable or reproducible. The board concludes that Wands' low rate of demonstrated success shows that a person skilled in the art would have to engage in undue experimentation in order to make antibodies that fall within the claims.

Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg [**25] binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. (Furthermore, since the two additional IgM antibodies for which the affinity constants were never measured showed binding in excess of 50,000 cpm, it is likely that these also fall within the claims.) Wands argues that the remaining 134 unanalyzed, stored cell lines should not be written off as failures. Instead, if anything, they represent partial success. Each of the stored hybridomas had been shown to produce a high-binding antibody specific for HBsAg. Many of these antibodies showed binding above 50,000 cpm and are thus highly likely to have a binding affinity constant of at least $10^{9.5}$ M⁻¹. Extrapolating from the nine hybridomas that were screened for isotype (and from what is well known in the monoclonal antibody art about isotype frequency), it is reasonable to assume that the stored cells include some that IgM. Thus, if the 134 incompletely analyzed cell lines are considered at all, they provide support (albeit without rigorous proof) to the view that hybridomas falling within the claims are not so rare that undue experimentation would be needed [**26] to make them.

The first four fusion attempts were failures, while high-binding antibodies were produced in the next six fusions. Appellants contend that the initial failures occurred because they had not yet learned to fuse cells successfully. Once they became skilled in the art, they invariably obtained numerous hybridomas that made high-binding antibodies against HBsAg and, in each fusion where they determined isotype and binding affinity they obtained hybridomas that fell within the claims.

Wands also submitted a second declaration under 37 C.F.R. § 1.132 stating that after the patent application was submitted they performed an eleventh fusion experiment and another hybridoma that made a high-affinity IgM anti-HBsAg antibody. No information was provided about the number of clones screened in that experiment. The board determined that, because there was no indication as to the number of hybridomas screened, this declaration had very little value. While we agree that it would have been preferable if Wands had included this information, the declaration does show that when appellants repeated their procedures they again obtained a hybridoma that produced an antibody that [**27] fit all

of the limitations of their claims.

We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures demonstrating that Wands' methods are unpredictable or unreliable. n29 At worst, they prove nothing at all about the probability of success, and merely show **[*740]** that appellants were prudent in not discarding cells that might someday prove useful. At best, they show that high-binding antibodies, the starting materials for IgM screening and Scatchard analysis, can be produced in large numbers. The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing, the less predictable the applicant's results become. Furthermore, Wands' explanation that the first four attempts at cell fusion failed only because they had not yet learned to perform fusions properly is reasonable in view of the fact that the next six fusions were all successful. The record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody **[**28]** art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens.

-----Footnotes-----

n29 Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.

-----End Footnotes-----

When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *In re Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening **[**29]** hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies **[**30]** against HBsAg, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure. n30

-----Footnotes-----

n30 *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

----- -End Footnotes-----

IV. Conclusion

Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. Accordingly, the rejection of Wands' claims for lack of enablement under 35 U.S.C. § 112, first paragraph, is reversed.

REVERSED

CONCURBY: NEWMAN (In Part)

DISSENTBY: NEWMAN (In Part)

DISSENT: NEWMAN, Circuit Judge, concurring in part, dissenting in part.

A

I concur in the court's holding that additional samples of hybridoma cell lines that produce these high-affinity IgM monoclonal antibodies need not be deposited. This invention, as described by Wands, is not a selection of a few rare cells from many possible cells. To the contrary, **[**31]** Wands states that all monoclonally produced IgM antibodies to hepatitis B surface antigen have the desired high avidity and other favorable properties, and that all are readily preparable by now-standard techniques.

Wands states that his United States Patent No. 4,271,145 describes fully operable techniques, and is distinguished from his **[*741]** first four failed experiments that are referred to in the Rule 132 affidavit. Wands argues that these biotechnological mechanisms are relatively well understood and that the preparations can be routinely duplicated by those of skill in this art, as in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947, 107 S. Ct. 1606, 94 L. Ed. 2d 792 (1987). I agree that it is not necessary that there be a deposit of multiple exemplars of a cell system that is readily reproduced by known, specifically identified techniques.

B

I would affirm the board's holding that Wands has not complied with 35 U.S.C. § 112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic **[**32]** claims. Wands' claims on appeal include the following:

19. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants, wherein said antibodies are coupled to an insoluble solid phase, and wherein the binding affinity constant of said antibodies for said HBsAg determinants is at least $10^{9} M^{-1}$.
26. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants wherein said antibodies are detectably labelled.

Wands states that he obtained 143 "high binding monoclonal antibodies of the right specificity" in the successful fusions; although he does not state how they were determined to be high binding or of the right specificity, for Wands also states that only nine of these 143 were tested.

Of these nine, four (three from one fusion and one from another fusion) were found to have the claimed high affinity and to be of the IgM isotype. Wands states that the other five were either of a different isotype or their affinities were not determined. (This latter statement also appears to contradict his statement that all 143 were "high binding".)

Wands argues that a "success rate of four out of nine", or 44.4%, is sufficient to **[**33]** support claims to the entire class. The Commissioner deems the success rate to be four out of 143, or 2.8%; to which Wands responds with statistical analysis as to how unlikely it is that Wands selected the only four out of 143 that worked. Wands did not, however, prove right point. The question is whether Wands, by testing nine out of 143 (the Commissioner points out that the randomness of the sample was not established), and finding that four out of the nine had the desired properties, has provided sufficient experimental support for the breadth of the requested claims, in the context that "experiments in genetic engineering produce, at best, unpredictable results", quoting from *Ex parte Forman*, 230 USPQ 546, 547 (Bd.Pat.App. and Int. 1986).

The premise of the patent system is that an inventor, having taught the world something it didn't know, is encouraged to make the product available for public and commercial benefit, by governmental grant of the right to exclude others from practice of that which the inventor has disclosed. The boundary defining the excludable subject matter must be carefully set: it must protect the inventor, so that commercial development **[**34]** is encouraged; but the claims must be commensurate with the inventor's contribution. Thus the specification and claims must meet the requirements of 35 U.S.C. § 112. *In re Fisher*, 57 C.C.P.A. 1099, 427 F.2d 833, 839, 166 USPQ 18, 23-24 (CCPA 1970).

As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112.

Wands is not claiming a particular, specified IgM antibody. He is claiming all such monoclonal antibodies in assay for hepatitis B surface antigen, based on his teaching that such antibodies have uniformly reproducible high avidity, free of the known **[*742]** disadvantages of IgM antibodies such as tendency to precipitate or aggregate. It is incumbent upon Wands to provide reasonable support for **[**35]** the proposed breadth of his claims. I agree with the Commissioner that four exemplars shown to have the desired properties, out of the 143, do not provide adequate support.

Wands argues that the law should not be "harsher" where routine experiments take a long time. However, what Wands is requesting is that the law be less harsh. As illustrated in extensive precedent on the question of how much experimentation is "undue", each case must be determined on its own facts. See, e.g., *W.L. Gore & Assocs., Inc. v. Garlock, Inc.* 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851, 105 S. Ct. 172, 83 L. Ed. 2d 107 (1984); *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); *In re Cook*, 58 C.C.P.A. 1049, 439 F.2d 730, 734-35, 169 USPQ 298, 302-03 (CCPA 1971).

The various criteria to be considered in determining whether undue experimentation is required are discussed in, for example, *Fields v. Conover*, 58 C.C.P.A. 1366, 443 F.2d 1386, 170 USPQ 276 (CCPA 1971); *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 USPQ 218 (CCPA 1965); *Ex parte Forman*, 230 USPQ at 547. **[**36]** Wands must provide sufficient data or authority to show that his results are reasonably predictable within the scope of the claimed generic invention, based on experiment and/or scientific theory. In my view he has not met this burden.

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